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Hegemann, S ; Straumann, D ; Bockisch, C

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Alexander's Law in Patients with Acute Vestibular Tone Asymmetry—Evidence for Multiple Horizontal Neural Integrators

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ABSTRACT

Alexander's law (AL) states that the slow-phase velocity of spontaneous nystagmus of peripheral vestibular origin is dependent on horizontal gaze position, with greater velocity when gaze is directed in the fast-phase direction. AL is thought to be a compensatory reaction resulting from adaptive changes in the horizontal ocular motor neural integrator. Until now, only horizontal eye movements have been investigated with respect to AL. Because spontaneous nystagmus usually includes vertical and torsional components, we asked whether horizontal gaze changes would have an effect on the 3D drift of spontaneous nystagmus and, thus, on the vertical/torsional neural integrator. We hypothesized that AL reduces all nystagmus components proportionally. Moreover, we questioned the classical theory of a single bilaterally organized horizontal integrator and searched for nonlinearities of AL implying a network of multiple integrators. Using dual scleral search coils, we measured AL in 17 patients with spontaneous nystagmus. Patients followed a pulsed laser dot at eye level jumping in 5° steps along the horizontal meridian between 25° right and left in otherwise complete darkness. AL was observed in 15 of 17 patients. Whereas individual patients typically showed a change of 3D-drift direction at different horizontal eye positions, the average change in direction was not different from zero. The strength of AL (= rate of change of total velocity with gaze position) correlated with nystagmus slow-phase velocity (Spearman's rho=0.5; $p<0.05$) and, on average, did not change the 3D nystagmus drift direction. In general, eye velocity did not vary linearly with eye position. Rather, there was a stronger dependence of velocity on horizontal position when subjects looked in the slow-phase direction compared to the fast-phase direction. We conclude that the theory of a simple leak of a single horizontal neural integrator is not sufficient to explain all aspects of AL.

Keywords: oculomotor, neural integrator, vestibulo-ocular reflex, nystagmus, adaptation

INTRODUCTION

Patients with an acute vestibular tone asymmetry (AVTA) show spontaneous nystagmus. The velocity of the slow phase of nystagmus is mainly determined by the difference of tonic vestibular activity between the right and left sides, with the eye drifting towards the side with a lower spontaneous activity (Leigh and Zee 2006). When the vestibular tone asymmetry is constant, the slow-phase velocity (SPV) of nystagmus should also be constant and the axis of eye rotation should not change depending on gaze position.

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However, the SPV in ongoing nystagmus varies depending on horizontal gaze position: SPV decreases when looking in the direction of the slow phase (Alexander 1912; Robinson et al. 1984). This behavior is called Alexander's law (AL).

Horizontal position dependency of eye velocity is not a natural feature of the rotational vestibular ocular reflex (VOR) (Robinson et al. 1984), so AL has been presumed to not arise in the peripheral vestibular apparatus, nor is it due to mechanical properties of the orbit. Hess (1982) and Robinson et al. (1984) suggested that AL results from adaptive changes in the neural mechanism that helps to ensure steady fixation at eccentric eye positions, which is necessary to counteract the elastic forces produced by extraocular structures. During eccentric fixation, elastic forces pull the eye back to a central position. A counter-acting force in the muscles is generated by integrating eye velocity commands, and so this mechanism is referred to as a neural integrator (NI) (Robinson 1968, 1975). If this neural integration is diminished, i.e., the time constant of the integrator is reduced, the NI is said to become "leaky" and the fixation command is insufficient to keep a normal eye from drifting back to a central position. This produces gaze-evoked nystagmus whose velocity increases with eccentricity. When combined with vestibular nystagmus, it reduces drift velocity in one direction, but increases velocity in the opposite direction, resulting in AL (Hess 1982; Robinson et al. 1984).

While the NI leak hypothesis is the most widely accepted mechanism for AL, it is not completely consistent with the eye velocity patterns seen in patients. According to the NI leak hypothesis, the change of velocity should be linear over the entire range of eye positions, although Alexander's original report (Alexander 1912), as well that of Hess (1983), describes different nystagmus patterns. Therefore, we sought to clarify these inconsistencies by measuring eye velocity with modern recording techniques in patients over a broad and finely sampled range of horizontal eye positions. Because spontaneous nystagmus of peripheral vestibular origin (SpN) is usually not purely horizontal but also includes vertical and torsional SPV, we further investigated if all nystagmus components are similarly affected, which would imply changes by the vertical/torsional NI. We asked specifically whether horizontal gaze changes would have an effect on the 3D drift of SpN. Finally, Robinson et al. (1984) reported that AL develops within about 25 s in normal people during caloric vestibular stimulation, suggesting a fast-acting adaptive mechanism. Thus, we also tested if the eye position dependency of nystagmus depends on the recent fixation history in patients.

METHOD

Patients

We investigated 17 patients, 10 women and 7 men, aged 21–71 years (mean 52) with an acute spontaneous nystagmus due to peripheral vestibular tone asymmetry (mean onset of vertigo 3.1 days before examination, range 0.25–13 days). All patients underwent a microscopic otoscopy and clinical neuro-otological examination. The clinical diagnosis of a peripheral vestibular tone asymmetry was made when a mixed horizontal torsional nystagmus was observed, no other acute neurological deficits could be detected, and the clinical head impulse test showed a hypofunction of the horizontal VOR with head rotations towards the direction of the slow phase of nystagmus. If no cause of the AVTA could be found, the diagnosis of idiopathic vestibulopathy was made (Table 1). Patients with Meniere's disease and spontaneous nystagmus due to vestibular migraine and patients with any acute neurological deficits other than cochleo-vestibular symptoms were excluded. The characteristics of the peripheral deficit (i.e., which canals were affected) were assessed by quantitative head impulse testing and caloric irrigation. The study adheres to the principles of the Declaration of Helsinki and was approved by the local ethics committee. Accordingly, all subjects gave their written informed consent after the experimental procedure had been explained. Inclusion criteria were an acute onset of vertigo within 14 days and a direction-specific spontaneous nystagmus.

Equipment

Eye and head movements were recorded in a magnetic frame (Remmel-type system, modified by A. Lasker, Baltimore, MD, USA) using dual scleral search coils (Skalar, Delft, the Netherlands) (Robinson 1963; Remmel 1984; Ferman et al. 1987). One search coil was placed on the right eye around the cornea after anesthetizing the conjunctiva with oxybuprocaine 0.4%; a second was tightly fixed on the forehead. Data was sampled at 1 kHz with 16-bit precision. Visual targets were produced by a laser, directed by a two-axis mirror galvanometer, which projected a 0.25°-diameter target on a tangent screen, 1.25 m from the subject. For measurements of nystagmus, the laser was pulsed (20 ms every 2 s) so that we could control the patient's gaze direction without visually suppressing nystagmus.

Procedure

Head impulse testing (Halmagyi and Curthoys 1988) was performed to determine the VOR gain in all

TABLE 1

Results of vestibular function tests: gain values for the VOR test as measured by head impulse testing in the SCC planes

Patient #	*Horizontal R/L*	*RALP/LARP down*	*RALP/LARP up*	*Caloric CP*	*Caloric DP*	*Clinical diagnosis*
1	*0.61*/**0.29**	0.78/**0.18**	*0.58*/**0.47**	**−37**	−16	IVP
2	NA	NA	NA	**50***	4*	Hemorrhagic otitis media
3	0.71/**0.46**	0.87/**0.38**	*0.64*/**0.47**	NA	NA	Hemorrhagic otitis media
4	0.79/**0.55**	NA	NA	−16	**−100**	IVP
5	**0.65**/0.83	**0.47**/0.71	0.92/0.88	**71**	−6	IVP
6	*0.60*/**0.43**	*0.58*/**0.52**	0.86/0.79	**−54**	**−38**	IVP
7	0.75/**0.44**	0.68/**0.31**	0.88/0.72	**−41**	**−46**	IVP
8	0.82/**0.28**	0.70/**0.28**	0.77/**0.44**	**−70**	**−49**	Temporal bone fracture
9	**0.33**/*0.49*	**0.20**/*0.47*	**0.60/0.53**	**53**	**77**	IVP
10	0.73/**0.35**	0.76/**0.17**	**0.47**/0.59	**−47**	**−100**	IVP
11	**0.41**/*0.56*	**0.35**/0.64	**0.64/0.54**	NA	NA	Traumatic perilymphatic fistula
12	0.99/**0.56**	0.89/**0.42**	1.01/0.76	**−55**	**−51**	IVP
13	1.04/**0.42**	1.05/0.65	0.86/0.84	NA	NA	IVP
14	0.77/**0.54**	*0.51*/**0.21**	0.87/0.91	NA	NA	IVP
15	0.74/**0.60**	0.89/0.68	0.70/0.79	**−51**	**−55**	IVP
16	0.88/**0.27**	0.77/**0.23**	0.66/0.82	**−63**	**−59**	IVP
17	**0.35**/*0.69*	**0.18**/*0.40*	**0.34**/*0.52*	**54**	**100**	IVP
Normal	≥0.71/0.70	≥0.69/0.54	≥0.67/0.68	≤+/−25	≤+/−30	IVP

Results of caloric tests are provided as canal paresis factor and directional preponderance according to the Jongkees formulas. Negative values represent hypofunction on the left horizontal SCC relative to the right horizontal SCC and preponderance of right beating nystagmus, respectively. Pathologic values are bold, and reduced gain values of the supposed intact side are in italics. Data with an asterisk are from a measurement 4 weeks after the onset of symptoms because initial testing was not possible due to acute otitis media

Horizontal R/L = horizontal plane, head movement towards right/left, respectively; RALP/LARP = plane of right anterior and left posterior SCC; down = head movement downwards in the respective plane testing mainly for anterior SCC function and up testing mainly for posterior SCC function; RALP = right-anterior left-posterior; LARP left-anterior right-posterior; CP = canal paresis factor; DP = directional preponderance; IVP = idiopathic vestibulopathy; NA = not available

canal planes (horizontal, right-anterior left-posterior, left-anterior right-posterior plane) and for both directions of each plane (Schmid-Priscoveanu et al. 1999). Briefly, patients fixated a target straight ahead, and the examiner stood behind the patient and manually induced short head movements with an amplitude of 10–20°. The mean peak velocities and accelerations were 342°/s and 12,442°/s^2 for horizontal movements, 214°/s and 7,118°/s^2 for movements in the on-directions of the anterior semicircular canals (SCCs), and 200°/s and 6,961°/s^2 for on-directions for the posterior SCCs. Gain was calculated as $\frac{1-\Delta\text{gaze}}{\Delta\text{head}(3°-7°)}$, where gaze (eye-in-space) and head were evaluated when the head had turned from 3° to 7°. A gain of +1 indicates perfect compensation (Palla and Straumann 2004).

Nystagmus was measured by instructing subjects to look in darkness at a pulsed target that moved every 5 s in steps of 5° from 25° right to 25° left and back. In a second trial – the jump paradigm – the flashing laser dot alternated between +/−25° eccentric positions every 20 s. This paradigm was performed in the first eight subjects to test for hysteresis, i.e., whether the previous position would influence the nystagmus velocity. Bithermal caloric vestibular testing was performed using a commercial caloric irrigator (Variotherm, Atmos MedizinTechnik GmbH & Co. KG, Lenzkirch, Germany). Both ears were irrigated for 30 s with 30 ml of water at temperatures of 44 and 30°C, respectively. For eye movement recording, we used a 50-Hz video-oculography system (VisualEyes, Micromedical™ Technologies, Chatham, IL, USA). Canal paresis factor and direction preponderance were calculated as relative differences in percentages in slow-phase eye velocity using the Jongkees formulas (Jongkees 1996). A canal paresis factor of 25% or more and a directional preponderance of 30% or more were regarded as pathologic.

Data analysis

Data were calibrated and processed using interactive programs written in MATLAB© (MathWorks, Natick, MA, USA). We computed rotation vectors and angular velocity as described previously (Hepp 1990; Tweed et al. 1990). We present data in the coordinates of the earth fixed coil frame with the z-axis aligned with gravity. Because the head of the subject was restrained with a chin rest, which kept Reid's line approximately parallel to the earth horizontal, the data represent a head fixed coordinate system, with positive rotations being clockwise, right, and up. We mirrored the horizontal and torsional data of the patients with right-side lesions, so all patients appear to have a left-side AVTA. There was no need to mirror the vertical data because the vertical components of the right and left anterior and right and left posterior SCCs are identical. All patients except one showed a downward drift.

Slow-phase eye velocity was found with an interactive computer program that first automatically detected saccades based on velocity and noise criteria (Holden et al. 1992) and then allowed the user to adjust the automatically marked saccades and to remove blink artifacts. Individual nystagmus slow phases were included in later analysis provided they were at least 100 ms in duration. For each slow phase, we calculated the median position and velocity for each component (horizontal, vertical, and torsional). For some graphs, we then averaged the slow-phase velocities and/or positions for each target direction, though all quantitative analysis was made without averaging over target positions.

We determined the linear change in eye velocity with horizontal gaze position with least-squares fits to the torsional, vertical, and horizontal eye velocity components, as well as to the total velocity (the length of the 3D eye velocity vector). Rank-order correlations were tested with Spearman's rho.

We analyzed the direction of nystagmus by decomposing the 3D eye velocity vector into two angles. We first projected the 3D velocity vector onto the plane defined by the horizontal and vertical components and calculated the angle of the projection in this plane. This angle varies from 0° (upward vertical velocity, with no horizontal component), to 90° (leftward, with no vertical component), to 180° (downward), to 270° (rightward). Likewise, we projected the vector on to the plane defined by the horizontal and torsional components, which gives an angle related to the horizontal/torsional direction: 0° is clockwise torsion, 90° is leftward, 180° is counterclockwise, and 270° is rightward. (The remaining direction in the torsional–vertical plane was ignored because subjects did not voluntarily change eye position in the vertical or torsional direction and the position change induced by the nystagmus was small.) When analyzed as a function of horizontal gaze position, this analysis provides us with information about how the direction of nystagmus, independent of the speed, varies with horizontal gaze position.

RESULTS

SCC lesion patterns

Table 1 shows the results of head impulse and caloric testing for each patient. One patient (#2) opted not to receive head impulse testing because of severe neck pain. In the remaining 16 patients, quantitative head impulse testing showed reduced gains for at least one horizontal canal (HC). Seven patients (44%) showed the pattern of a so-called superior vestibular neuropathy, with the HC and anterior canal (AC) affected but the posterior canal spared, and seven (44%) had a complete vestibulopathy with all SCCs affected. Two patients (13%) had an isolated HC defect only. The vertical canals were not tested in one patient (#4). In 11 patients, the gain reduction of the HC was unilateral. In five patients, HC gain reduction was bilateral, but in all patients the HC gains were reduced asymmetrically with the gain on the weaker side at least 20% decreased relative to the other side. Spontaneous nystagmus was consistently beating towards the side with the higher gain.

Caloric irrigation revealed a vestibular tone asymmetry in all patients tested. Five patients could not be tested in the initial phase, two (#2 and #3) because of an acute hemorrhagic otitis media and one (#11) because of a traumatic perilymphatic fistula. The latter was asymptomatic the day after closure of the perilymphatic fistula on the side with the weaker gain. Patient 2 had neither an initial head impulse nor caloric testing but was tested 4 weeks later by caloric irrigation showing a canal paresis factor of 50%. Two patients refused caloric testing.

In summary, 12 patients had an AVTA with a relative hypofunction on the left and 5 on the right side. Seven patients had a vestibular loss with affection of all three SCCs, seven showed the pattern of a superior vestibular neuritis (HC and AC affected), and two patients had a lesion of the lateral SCC canal only.

Drift direction of nystagmus slow phase in relation to the lesion pattern

The horizontal drift component (the slow-phase direction) was always towards the weaker HC according to head impulse and caloric testing, as expected. Horizontal drift velocity at gaze straight ahead ranged from −1 to −14°/s with a mean of −6.5°/s. All patients except one had a downward slow-phase drift. Vertical drift velocities ranged from 0.2 to −6°/s (mean: −2.2°/s). The patient with the upward slow-phase drift (#8) had the weakest vertical drift velocity. Torsional SPV was between 0.5 and 20°/s, and the direction was always counter-clockwise. Figure 1 shows the axis of rotation of the nystagmus slow phase for straight-ahead gaze for each patient normalized by the velocity magnitude. The axes thus show nystagmus direction. Also shown are the ocular motor rotation axes associated with excitatory stimulation of each SCC, which were derived according to the anatomical measurements of Della Santina et al. (2005). The nystagmus rotation axes cluster near the excitatory direction of the right horizontal SCC or opposite the direction of the weaker, left horizontal SCC. The axes also deviate slightly to oppose the left anterior SCC.

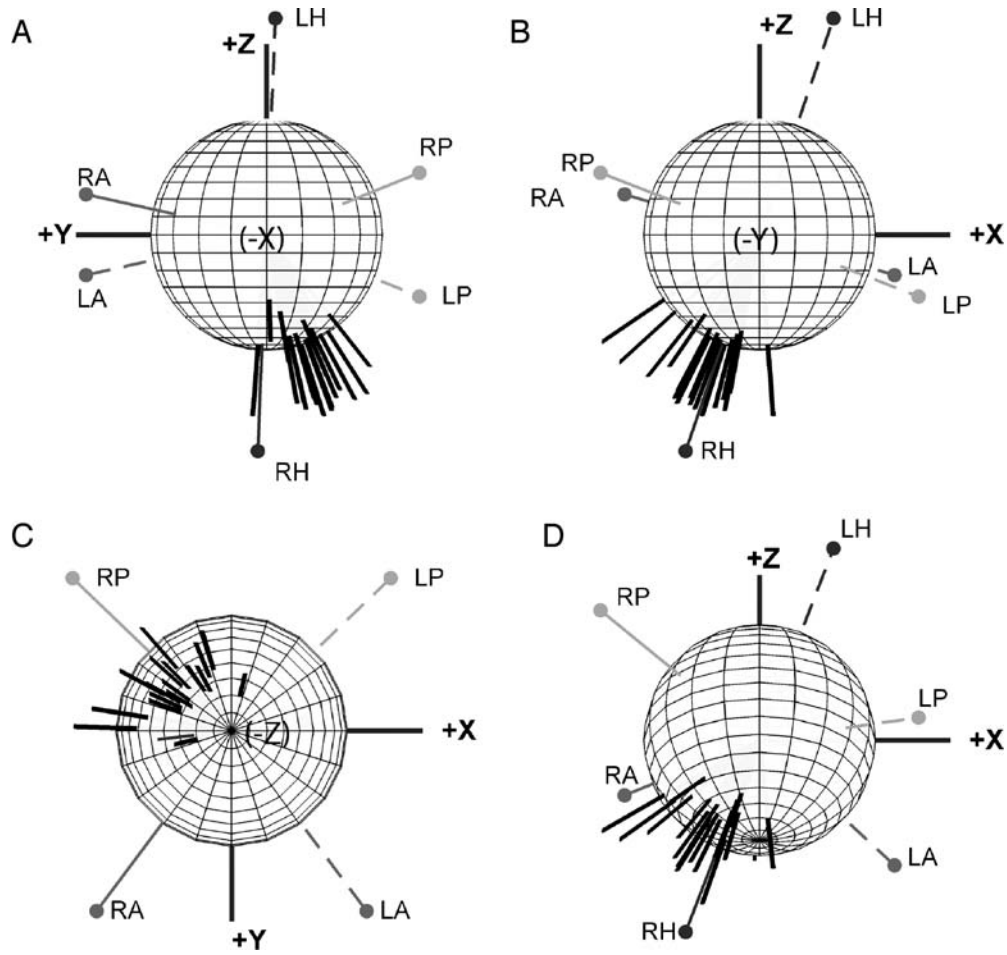

FIG. 1. The axes of eye velocity (*black lines*) are shown for each patient at straight-ahead gaze (intercept of linear fits to the velocity vs. position data), normalized by the velocity magnitude. The orientations of the axes thus show drift direction. Also shown are the oculomotor rotation axes associated with excitatory stimulation of each SCC [*L*(*R*)*H* = left (right) horizontal, *LP* = left posterior, *LA* = left anterior]. The Y-axis is aligned with Reid's line with a positive direction to the right, X and Z are normal to Reid's line with forward and upward directions positive. Each plot, **A**–**D**, shows the same data from different viewpoints: **A** view from behind (−X); **B** view from the left (−Y); **C** view from below (−Z); **D** view from a left-low-posterior position.

Dependence of slow-phase drift velocity on gaze position

Figure 2 shows representative data from three patients. The top panel shows eye position as a patient (#9) followed the flashing target from 25° left to 25° right. The right-beating nystagmus when looking left is weaker then when looking to the right, that is, the nystagmus is stronger in the direction of the fast phase in accord with AL. Figure 2A also shows nystagmus in both vertical and torsional eye position. In Figure 2B, the median eye velocity of each slow phase is shown, as a function of horizontal eye position, for the same patient. This patient shows a linear dependence of horizontal velocity on horizontal gaze position, with a peak velocity of about −12°/s when looking 25° right, which declined to about −2°/s when looking 25° left. In our patients, we never observed a reversal of the direction of horizontal eye velocity, as reported by Hess (1983), although this might be because we only measured to 25° eccentricity. In addition, Figure 2B shows the vertical and torsional velocity of the slow phases, which also show a clear linear dependence of eye velocity on horizontal gaze position. Figure 2C and D show different patterns of results from two different patients. In Figure 2C (#6), while eye velocity is apparent in all three directions, there is very little change in velocity with horizontal gaze position. The patient in Figure 2D (#15) showed a constant change in eye velocity when looking left, although in rightward gaze there is less of a change in eye velocity.

As represented in Figure 2, the patients typically showed downward and counterclockwise drift (upper pole rolls towards patients left side), in addition to the leftward horizontal component. These components are expected from a vestibular disturbance from the left HC with or without involvement of the anterior SCC as explained above. We used linear

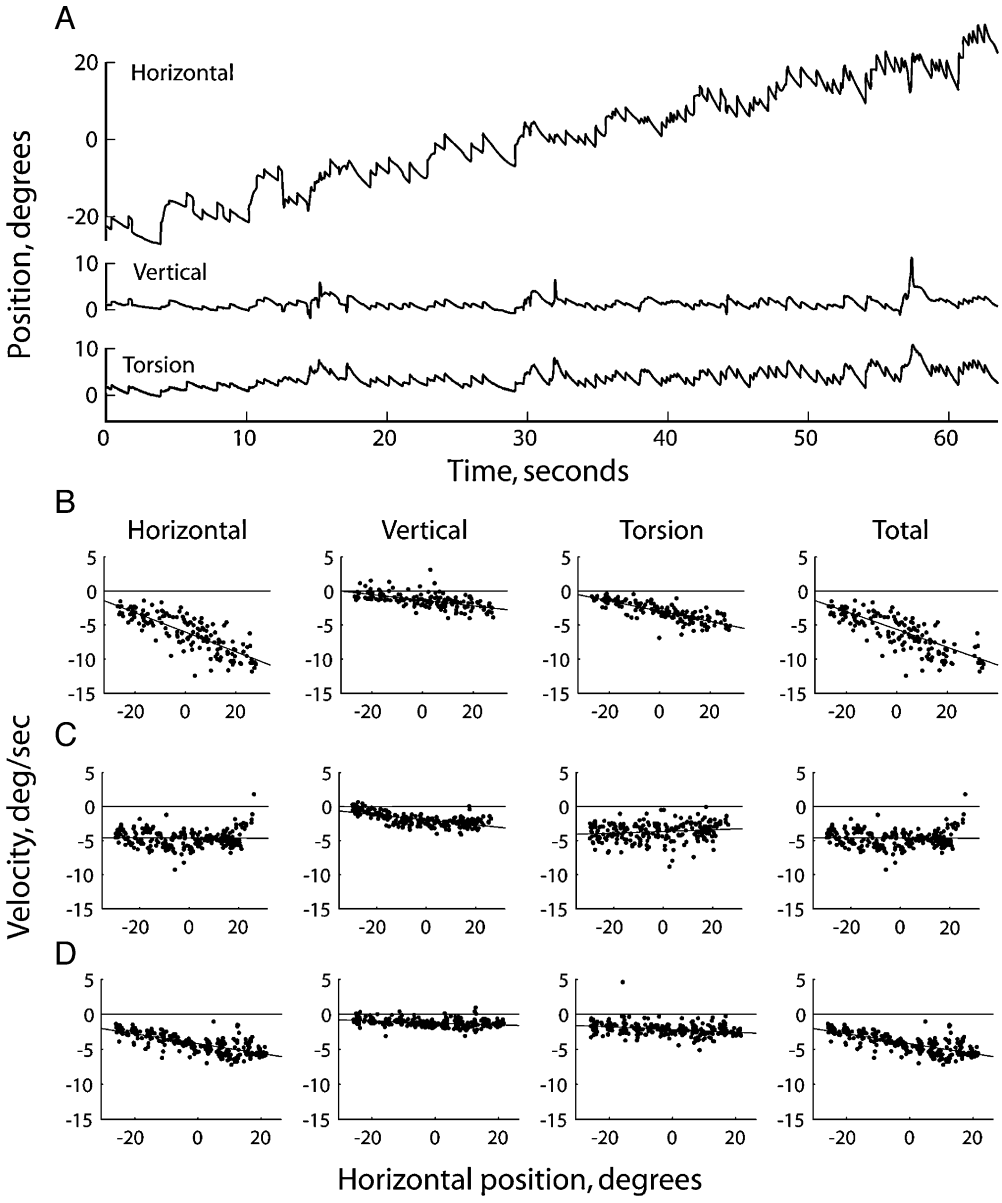

FIG. 2. **A** Horizontal, vertical, and torsional eye position as a patient (#9) followed a flashing target that moved from 25° left to 25° right. For horizontal position, the eye drifts slowly to the left, and a saccade redirects gaze to the right. **B** The median eye velocities for each slow phase are shown from the same patient as in **A**, including an additional "sweep" as the target moved right-to-left that is not shown in **A**. Horizontal, vertical, and torsional eye velocity are all greatest for rightward gaze. The best-fit regression lines are also shown. **C** A second patient (#6), where horizontal eye velocity is constant with horizontal gaze position but vertical eye velocity shows a small change with velocity being greatest for gaze to the right. **D** A third patient (#15), where horizontal eye velocity is linearly increasing from 25 degrees left to about 5 degrees right gaze, but on further right gaze one gets the impression that velocity change is reduced.

regression to characterize the change in horizontal, vertical, torsional, and total velocity on horizontal eye position (see Fig. 2). Fifteen of 17 patients showed a significant change in horizontal velocity with horizontal position that was consistent with AL (all ps<0.05). The average slope of the linear fits was −0.1°/s per degree of horizontal position, and the average bias (intercept), which indicates horizontal eye velocity at gaze straight ahead, was −6.5°/s. Both the average slope and bias were significantly different from zero (t tests: slope t=7.8, p<0.01; bias t=4.8°/s, p<0.01). The average slope of −0.1 corresponds to a NI time constant of 10 s (time constant=1/slope), whereas normal values are measured between 15 and 70 s (Becker and Klein 1973; Hess et al. 1985). Most patients also showed significant changes in vertical (16 of 17) and torsional (13 of 17) velocity with horizontal position. For vertical velocity, the average bias was −2.2 (t=5.2, p<0.01) and the average slope was −0.043 (t=3.0; p<0.01). For torsional velocity, the average bias was −3.5 (t=3.0, p<0.01) and the average slope was −0.034 (t=2.3; p<0.05). The average slopes

of the change in torsional, vertical, and horizontal eye velocity were such that, in general, eye velocity in all components decreased when the patients looked to the left.

If the change in eye velocity with gaze position is an adaptive response to the vestibular induced nystagmus, one would expect the strength of the effect to depend on the magnitude of the nystagmus. Figure 3 shows these relationships, taking the bias of the fits of total velocity vs. gaze position (the "total bias") as an estimate of the vestibular contribution to the nystagmus. The correlation between the horizontal slope and the bias was significant (Spearman's rho=0.5; t=2.3; p<0.05). The correlation between vertical slope and total bias was also significant, (rho=0.57; t=2.7; p<0.05), whereas the torsional slope was not (rho=0.16; t=0.62; p>0.5). The slope for total eye velocity was significantly correlated with the total bias (rho=0.53; t=2.4; p<0.05).

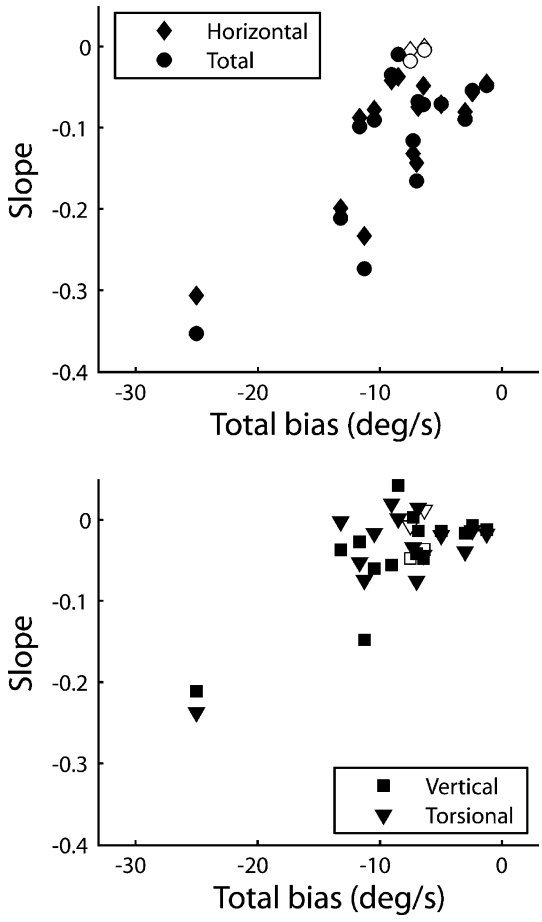

FIG. 3. The strength of AL varies with nystagmus intensity. *Top*: The slopes of the best-fit lines of horizontal and total eye velocity vs. the horizontal position are plotted vs. the total eye velocity bias. The sign of the total bias, and the slope for total velocity, have been inverted to facilitate comparison with the horizontal data. The total bias is the total 3D velocity at gaze straight ahead. Each *symbol* represents a single patient, and *filled symbols* indicate those patients who showed a statistically significant AL. *Bottom*: The slopes of the best-fit lines of vertical and torsional eye velocity vs. the horizontal position are plotted vs. the total eye velocity.

No hysteresis

The "jump" paradigm was designed to find hysteresis in eye velocity by having the patients alternate gaze between +25° and −25°. We performed this analysis on the first eight patients and found no difference in either the slope or bias for horizontal, vertical, torsional, or total eye velocity compared to our standard protocol. (Horizontal differences: bias=0.05°/s, paired t=0.1, p=0.9; slope=−0.02, t=0.88; p<0.5; all other components showed similarly small, statistically insignificant differences.) Because we did not find any hysteresis, we stopped testing for hysteresis to reduce the test duration.

Drift direction

For our patients with a relative left-hypofunction, eye drift for gaze straight ahead was left, down, and counterclockwise. However, the direction could change depending upon horizontal gaze position. Figure 4A, B shows an example of the direction of drift in the horizontal/vertical and horizontal/torsional planes. In this patient (#11), the downward component seen in right gaze (the fast-phase direction) disappears (and may even change to an upward component) in left gaze (Fig. 4A). Figure 4C shows the drift orientation in the same patient as a function of horizontal eye position. Zero-orientation indicates up (for the horizontal/vertical plane) and clockwise (for the horizontal/torsional plane), respectively, and 90° indicates left. Best fit lines to this data are shown. The vertical component becomes relatively smaller in the slow-phase direction (positive slope), or, in other words, the dependence of velocity on horizontal eye position is relatively stronger for vertical compared to horizontal velocity. The torsional component tends to be relatively larger in left gaze, and thus, the slope of the orientation vs. horizontal position is negative. The histograms in Figure 4D show the change in orientation of the slow-phase drift, that is, the slopes of the best fit lines of orientation vs. horizontal position such as those in Figure 4C. The maximum slope was about 1.4, which means that the nystagmus of this patient changed its direction by 14 degrees when the patient changed horizontal gaze position by 10 degrees.

In most patients, drift direction varied significantly with horizontal gaze position. We computed linear fits of the drift direction orientation vs. horizontal eye position, and in the horizontal–vertical plane, 14 of 17 (82%) patients showed a significant change in

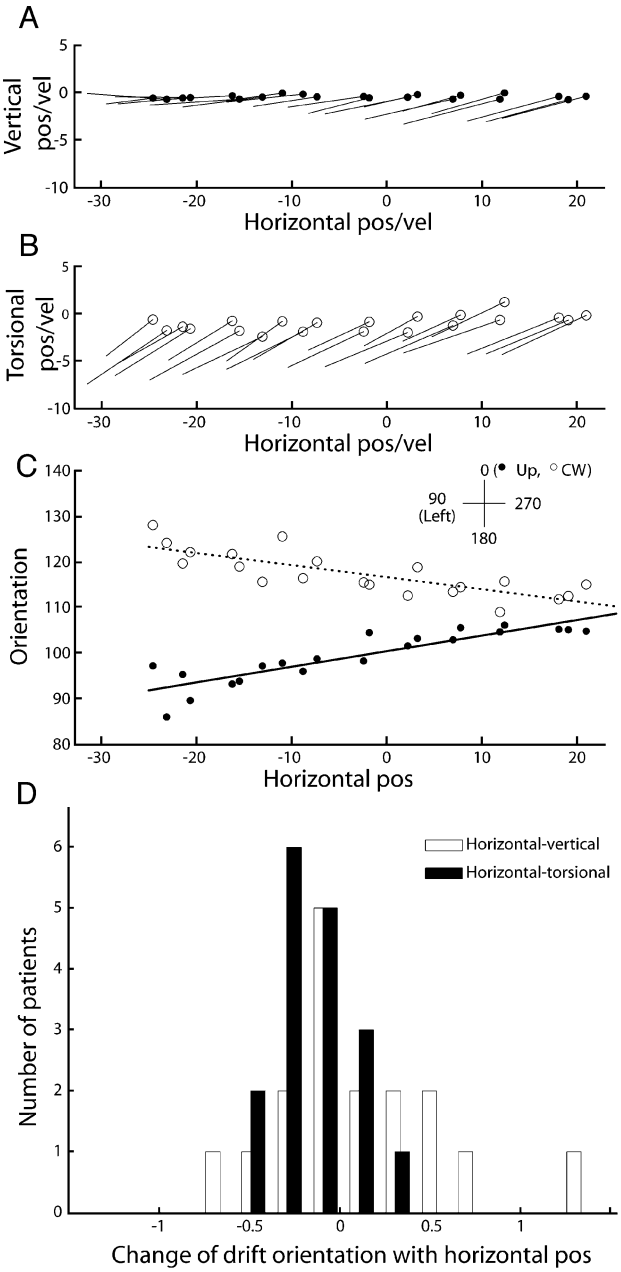

FIG. 4. Slow-phase drift direction could change with horizontal eye velocity. **A–C** Data from patient #11. **A** Each point shows the average horizontal and vertical eye position during each fixation period. The line extending from each point indicates the average horizontal and vertical velocity for that fixation period. Thus, the orientation of the line gives the direction of nystagmus in the horizontal/vertical plane, and the length is the magnitude. **B** Torsional and horizontal position and velocity. **C** The direction of nystagmus in the horizontal–torsional direction (*solid symbols*) and horizontal–vertical direction (*open*) is shown relative to horizontal position for the same patient, along with the best-fit lines. **D** Histograms showing the change in orientation of the slow-phase drift for the horizontal–vertical direction (*open bars*) and horizontal–torsional direction (*solid bars*) for all patients. These are the slopes from linear fits, such as in **C**.

drift direction. In the horizontal–torsional plane, 10 of 17 patients (59%) showed a significant change in drift direction with horizontal eye position. Only two patients (12%) showed no change in drift direction in both planes. Note that these were not identical with the two patients who showed no AL in the horizontal velocity component.

If AL modulates drift velocity, the direction of drift will remain constant if and only if the change in velocity is proportional in all components. In Figure 4A, the vertical component changes more, proportionally, than the horizontal component, leading to a change in drift direction. In Figure 4B, the changes in horizontal and torsional component are closer, so a change in the horizontal–torsional difference is less obvious. This is clearer in Figure 4C, where the slope of the best-fit horizontal–vertical line is greater than the horizontal–torsional line.

Despite significant changes of drift direction in individual patients, there was no consistent pattern of direction change. Thus, for the whole group, the average change in direction (the slope of best fit line for direction and gaze position) was not significantly different from zero for both the horizontal–vertical plane (mean=0.075; t=0.6; p=0.5) and the horizontal–torsional plane (mean=−0.1; t=1.9; p<0.08) (Fig. 4D).

Gaze dependent changes in the slope of velocity vs. position

We frequently observed that the change of eye velocity with eye position was not constant but could be different depending upon whether the patient was looking to the left or to the right. Figure 5B and C provide two such examples. We fit separate lines to eye velocity depending upon whether the patient was looking to the left or right of straight ahead. Figure 5A (#9) shows an example where the slopes of the two lines were very similar. In Figure 5B (#2), when the patient looked in the positive direction, where eye velocity was higher, there was little change in velocity with position, in contrast to the negative direction. Figure 5C (#6) shows a more extreme example, where the change in velocity reverses direction. Averaged over all patients, the slope for gaze in the slow-phase direction was −0.14, whereas the slope for gaze in the fast-phase direction was −0.04, a difference that was significant (paired t=2.6, p<0.05). We found that 15 of 17 patients (88%) showed a significant decrease in horizontal velocity with horizontal position when looking in the slow-phase direction. In the fast-phase direction, nine patients showed a significant negative slope, three (numbers 4, 6, and 13) showed a significant positive slope, and five (numbers 2, 3, 12, 15, and 16) showed a slope that was not significantly different from 0. Figure 5D shows the parameters of the linear fits of the horizontal

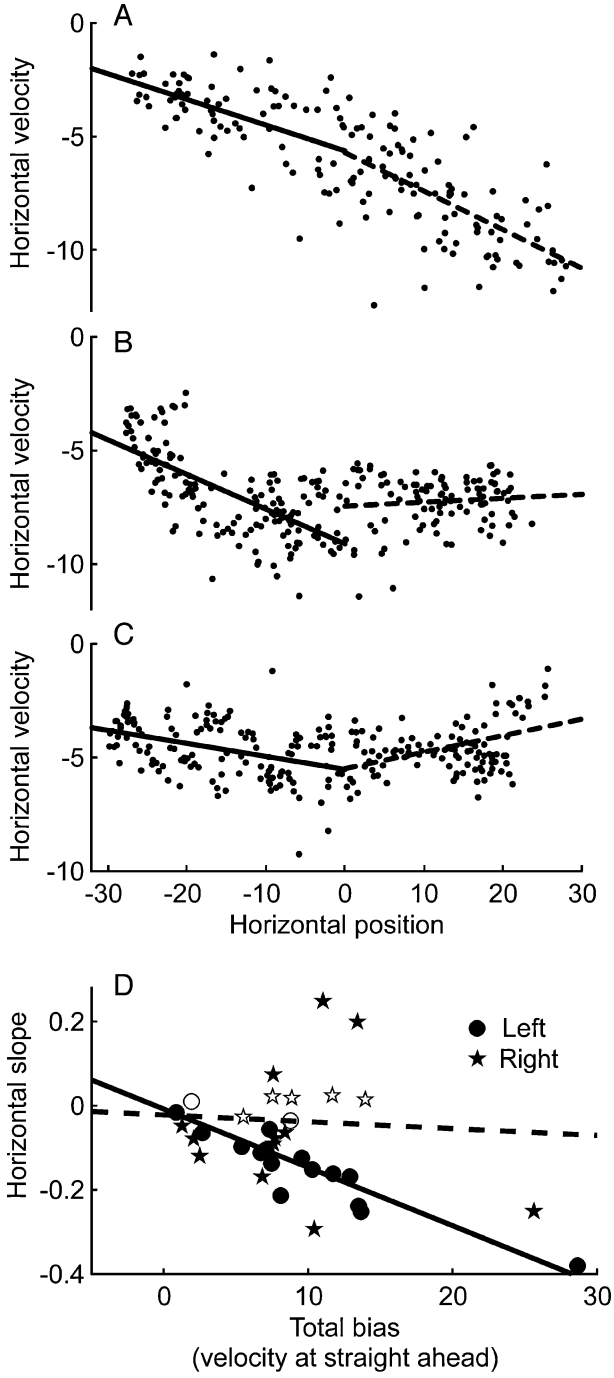

FIG. 5. The change in eye velocity with position could be different depending upon whether the subject was looking in the slow-phase direction or the fast-phase direction. **A–C** Data from different patients. *Solid lines* indicate the best-fit lines to the velocity data when subjects looked to the left, *dashed lines* show the best-fit lines for eye positions to the right. The two slopes for the patient in **A** (#9) show little difference, whereas in **B** (#2), eye velocity when looking to the right is mostly unchanged, and in **C** (#6), the slope of the best-fit line changes direction. **D** The slope-values of each best-fit line to horizontal velocity for the left and right hemifield for all patients are plotted against the total eye velocity, showing that, in left gaze, the slope of AL increases with the total eye velocity, but not in right gaze. *Circles* indicate data when patients looked to the left and *stars* indicate data when they looked to the right. *Solid symbols* indicate slopes that were significantly different from zero.

slopes vs. the total eye velocity. When looking left (in the slow-phase direction), the slope of the best-fit line increases with the total bias (slope=0.014; R^2=0.8; p<0.01), whereas when looking to the right, the slope does not consistently vary with the total bias (slope=−0.002, R^2=0.004, p>0.7). We also calculated Spearman's rho, a nonparametric correlation measure, for velocity axes vs. the total eye velocity. When looking in the slow-phase direction, horizontal, vertical, and total velocity components showed significant correlations with the total bias (all ps<0.01), but the change in torsional velocity with horizontal eye position was not correlated with the total bias (p>0.3). When looking in the fast-phase direction, all correlations were not significant (all p values>0.18).

Finally, we analyzed whether the direction of the slow phase varied with eye position, similar to the analysis in Figure 4, when looking to the left, where we observed stronger AL. The average change in direction (the slope of best fit line for direction and gaze position) was not significantly different from zero for both the horizontal–vertical direction (mean=−0.08; t=0.5; p>0.6) and the horizontal–torsional direction (mean=−0.1; t=1.3; p>0.1).

DISCUSSION

We measured the effect of horizontal gaze position on eye velocity and drift direction in patients with AVTA, as determined by head impulse testing and bithermal caloric testing. For the first time, we described the effects of horizontal eye position changes on 3D velocity and drift direction changes. We found that the strength of AL, the gaze-dependent change of eye velocity, increased in patients with higher nystagmus velocity. This is consistent with the view that AL is a compensatory reaction that reduces nystagmus SPV in one direction of gaze so that retinal image slip is minimized. Since the studies by Hess (1982) and Robinson et al. (1984), it has been assumed that AL is a consequence of a single horizontal NI becoming leaky, that is, the normal force command needed to maintain an eccentric horizontal eye position is reduced. Below, we consider how our results require modification of this view.

Unilateral vestibular deficit vs. asymmetric bilateral hypofunction

We found bilateral – although asymmetric – VOR gain reductions during head impulse testing in 7 of 17 patients. Although concomitant VOR gain reduction with head impulses towards the supposed healthy side is known in patients with acute unilateral peripheral vestibulopathy (Aw et al. 2001; Halmagyi

et al. 1990; Palla and Straumann 2004), we cannot exclude a bilateral asymmetric affection in these patients. AL was observed in all of these patients, and a difference between unilateral and asymmetric bilateral hypofunction has never been made in the literature with respect to AL. Thus, we think it is reasonable to not distinguish between pure unilateral hypofunction and asymmetric bilateral hypofunction here.

No hysteresis

By comparing small, stepwise position changes with large gaze jumps, we tested the hypothesis that AL is dependent on the eye position immediately preceding the new position. Robinson et al. (1984) reported that, in normal subjects with nystagmus induced with calorics, AL can develop in ~25 s with the sudden onset of nystagmus. We found no hysteresis, i.e., no evidence for any fast-acting adaptation process, perhaps because the response to calorics is different or the adaptation process in patients that have experienced an abnormal vestibular stimulus for at least many hours is different from the initial adaptive response.

Dependence of vertical and torsional eye velocity and nystagmus direction on horizontal eye position

Studies of AL have typically been limited to descriptions of horizontal eye velocity, although nystagmus resulting from vestibular lesions is more complex, usually containing vertical and torsional components, as well. An unexpected finding was that, in our AVTA patients, the vertical and torsional nystagmus decreased when they looked in the direction of the horizontal slow phase. This could occur if the vertical–torsional NI was sensitive to horizontal eye position, and adapted as well. Static torsional position does vary with horizontal position when the head is pitched forward or backward (Haslwanter et al. 1992; Bockisch et al. 2001; Furman and Schor 2003); if this torsional command passes through the common torsional–vertical NI, then the torsional–vertical NI must be sensitive to horizontal gaze position.

Our patients typically had downward and counterclockwise drift in addition to the dominant horizontal component, and all three typically modulated with horizontal gaze position. In 82% of patients, the direction of nystagmus varied significantly with eye position, but the changes were not consistently in the same direction, and so across patients the average change in direction was not different from zero. An explanation of this finding might be that changes in the horizontal and vertical/torsional NI are not rigidly coupled but show individual variations, and in general, both integrators work together to reduce the horizontal, vertical, and torsional nystagmus components in approximately equal proportions.

Multiple horizontal NIs

Superimposing a gaze-evoked nystagmus (where the eye drifts back towards a central orbital position) on to the vestibular evoked nystagmus decreases eye velocity in the slow-phase direction but has the unfortunate consequence of increasing eye velocity in the fast-phase direction. A more adaptive response, in terms of reducing the vestibular nystagmus, would be for the NI to become unstable in the fast-phase direction, that is, to produce a gaze-evoked nystagmus that would normally push the eye to eccentric positions. Indeed, we observed this behavior in three patients (Fig. 5C). In general, we found that eye velocity varied more with gaze position when patients looked in the fast-phase direction compared to when they looked in the slow-phase direction. This means that the NI has the ability to differentially adapt to gaze directions, suggesting that there are functionally separate integrators for left and right gaze. The diverse patterns of behavior seen in Figure 5 can be explained as arising from the relative amounts of adaptation for left and right gaze: the integrators for positions in the phase-fast direction become leaky, while those in the slow-phase direction can become similarly leaky (Fig. 5A), unchanged (Fig. 5B), or unstable (Fig. 5C). Cannon et al. (1983) introduced the concept of multiple integrators in their neural network model of the NI to improve the network's stability. Crawford and Vilis (1993) provided evidence for multiple vertical/torsional integrators when they pharmacologically inhibited the integrator and found that the eye did not drift to a single resting position, but rather, multiple resting positions were possible. Recent experimental findings in goldfish also support the hypothesis of separate integrators for horizontal gaze (Aksay et al. 2007).

CONCLUSION

AL is frequently observed in AVTA patients and has traditionally been explained as a simple change in the horizontal NI. Our measurements of the 3D eye movements in AVTA patients suggest the mechanism of AL, while still perhaps based on brainstem and cerebellar NIs, might not be as simple as originally thought. Our data lend support to the idea of multiple horizontal NIs adapting differentially to the vestibular tone asymmetry. Furthermore, we showed that horizontal eye position influences both the horizontal and vertical/torsional NI.

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